REMARKS

Claims 172, 175-181 and 183-191 are currently pending and presented for examination. Applicants have hereinabove added new claims 192-194. In addition, applicants have hereinabove cancelled claims 131-171, 173, 174, and 182 without prejudice or disclaimer to applicants' right to pursue the subject matter of these claims in the future. Support for new claim 192 can be found *inter alia* in the description as filed at page 18, lines 10-17. Support for new claims 193 and 194 can be found *inter alia* in the description as filed at page 4, lines 25-29; page 12, lines 11 and 12; page 18, lines 4-7; page 19, lines 6-8; and page 39, line 4 to page 41, line 10. Applicants submit that new claims 192-194 introduce no new subject matter and are fully supported by the application as originally filed.

In addition, applicants have hereinabove amended claims 172, 175, 177-179, 184, and 187-191. Support for amended claim 172 can be found *inter alia* in the description as filed at page 4, lines 19-23 and page 4, line 31 to page 5, line 3. Support for claims 175, and 177-179 can be found *inter alia* in the description as filed at page 18, line 30 and page 19, line 8 and lines 19-21. Support for amended claim 184 can be found *inter alia* in the description as filed at page 17, lines 28-32. Support for claims 187-191 can be found *inter alia* in the description as filed at page 18, line 30 and page 19, line 8 and lines 19-21. Applicants submit that amended claims 172, 175, 177-179, 184, and 187-191 introduce no new subject matter and are fully supported by the application as originally filed. Accordingly, after entry of this Amendment claims 172, 175-181 and 183-194 will be pending in this application.

Applicants have amended the Specification at pages 39-43 to correct the inadvertent errors in the references to certain figure numbers in the specification. These amendments are

supported by the Specification as filed at pages 10-11 and pages 39-43, and in Figures 15-23 themselves as filed.

Rejection Under 35 U.S.C. §112 - Enablement

In the November 13, 2008 Office Action, the Examiner alleged that the specification fails to provide sufficient teachings to enable the invention defined in claims 172, 175-181 and 183-191. The Examiner acknowledged that the specification enables a method of inducing neovascularization by a direct injection of mesenchymal precursor cells (MPCs) from bone marrow that express STRO-1. However, the Examiner asserted that it is unpredictable to extrapolate from the enabled subject matter to the administration of cells from any source by any route to practice the invention.

In the enablement rejection, the Examiner also indicated that the figures cited in the specification in paragraphs 0147 to 0148 do not support the teachings in the specification at paragraphs 0147 to 0148.

Applicants' Response

Figures

With regard to the Examiner's assertion on page 4 of the Office Action that the figures in the specification are inconsistent with the reported observations, applicants have hereinabove corrected inadvertent errors in the numbering of the figures referred to. As such, the recited figures are now consistent with the reported observations.

Applicants respectfully traverse the Examiner's rejection. Applicants respectfully submit that the specification teaches a variety of methods for isolating STRO-1 expressing cells from a variety of tissue sources, e.g., at page 20, line 4 to page 21, line 15. Moreover, the specification exemplifies isolation and

culture of STRO-1 expressing cells from a variety of tissues, e.g., bone marrow, dental pulp, peripheral adipose and skin. The specification also teaches detection of cells expressing STRO-1 and other markers expressed by the cells that have been isolated from spleen, pancreas, brain, kidney, liver and heart. Furthermore, the specification demonstrates that STRO-1 expressing cells from bone marrow, dental pulp, and adipose tissue are capable of differentiating into a variety of tissues such as bone, fat, cartilage and vascular tissues e.g. arterioles and other blood vessels, as indicated on page 17, lines 9-11; page 36, lines 14-16; page 38, lines 8-14 and page 39, line 1 to page 41, line 9. The specification additionally teaches a variety of means for formulating and/or administering the isolated and/or cultured cells, e.g., as page 12, line 28 to page 16, line 11, and clearly exemplifies the administration of STRO-1 expressing cells to tissues to induce production/repair of blood vessels, e.g., at page 39, line 1 to page 41, line 9. Accordingly, the specification demonstrates that STRO-1 expressing cells exist in at least nine different tissues and can be isolated and/or cultured from at least four of those tissues. The specification also teaches that the cultured cells can differentiate into a variety of different cell types and that administration of STRO-1 expressing cells induces production of blood vessels.

Applicants submit herewith a publication by Finney et al., *Biol. Blood and Marrow Transplant.*, 12: 585-593, 2006 (appended hereto as **Exhibit 1**). This document teaches isolation of endothelial progenitor cells from bone marrow or umbilical cord blood. About 20% of the cells express STRO-1 (see Figure 2). The authors also demonstrate that intracardiac administration of the cells to subjects suffering from lower limb ischemia induced by femoral artery ligation. As shown in Figure 3, cells treated with STRO-1 expressing cells show better perfusion in a shorter period than control animals, and tissue from the gastrocnemius (calf muscle) had significantly more capillaries per square millimeter in

subjects treated with STRO-1 expressing cells than control animals. Accordingly, this publication demonstrates that STRO-1 expressing cells other than MPCs can be used to induce blood vessel formation/repair and that STRO-1 expressing cells can induce blood vessel formation/repair at sites remote to the site of administration.

As for the Examiner's reliance on Barry et al. *Birth Defects Res.*, 69: 250-256, 2003; Kassem et al., *Cloning Stem Cells*, 6: 369-374, 2004; Le Blanc et al., *Biol. Blood and Marrow Transplant.*, 11: 321-334, 2005; and Summer et al., *Proc. Am. Soc.*, 5: 707-710, 2008 to allege that the state of the art is "unpredictable," applicants respectfully submit that the discussion hereinabove and the *in vivo* experiments conducted by the applicants and others demonstrate that applicants have provided sufficient teachings to enable the full scope of the subject matter claimed. Moreover, Barry et al.'s comments regarding understanding "the mechanism underlying stem cell therapies" (emphasis added) are not germane to whether one can make and use the claimed invention which is supported by a working example. The exact mechanism underlying the action is not needed for enablement. In addition, Le Blanc et al.'s comments regarding *in vitro* data are not relevant to the claimed method which is supported by the *in vivo* working example in the specification. Furthermore, the speculation in Le Blanc et al. cited by the Examiner on page 5 of the Office Action regarding the mechanism underlying the observed clinical effect of MSCs is again not germane to whether the specification enables one skilled in the art to make and use the claimed invention. The exact mechanism underlying the action is not needed for enablement.

Based on the foregoing, applicants maintain that the invention as claimed is enabled and respectfully request the Examiner to reconsider and withdraw this rejection.

Rejection Under 35 U.S.C. § 102 - Novelty

The Examiner asserted that claims 172, 175-181 and 183-192 are anticipated by Chopp et al. (*The Lance Neurology*, 1: 92-100, 2002). In particular, the Examiner asserted that Chopp et al. discloses methods that result in angiogenesis or vasculogenesis following treatment of a neural injury with bone marrow stromal cells including mesenchymal stem cells (MSCs) (Abstract; p96-98 and Figure 3). The Examiner also asserted that the MSCs taught in Chopp et al. inherently express STRO-1 and that this was known at the time of the instant invention.

Applicants' Response

Applicants respectfully traverse the Examiner's rejection. Applicants initially point out that Chopp et al. is a review article that sets out the *theories* of the authors and reviews some literature that the authors consider support for those theories. For example, at page 96, right-hand column clearly states "Our *operational hypothesis* is that therapeutic benefit [of MSCs] is induced by a series of events..." (emphasis added).

Applicants submit that the Examiner has incorrectly concluded that the cells described in Chopp et al., inherently express STRO-1. As the Examiner has correctly stated at page 6 of the pending Office Action, the teachings in Chopp et al., are in respect of mesenchymal *stem* cells. This is apparent from the teachings in the final paragraph at page 96, right hand column of Chopp et al. describing experiments making use of, and distinguishing between, "MSC supernatant or MSC themselves" and in Figures 2 and 3, which explicitly refer to MSCs. In regard to this, applicants respectfully direct the Examiner's attention to the disclosure in Table 1 on page 44 of the instant application, which distinguishes between MSCs and MPCs, and which shows that

MSCs *do not* express detectable levels of STRO-1. Thus, in contrast to Chopp et al., the present invention relates to enriched populations of cells expressing STRO-1, including mesenchymal precursor cells (e.g. see claims 175-179). Given that Chopp et al. provide no description of the cell surface markers expressed on their MSCs, and applicants not observing STRO-1 on MSCs (as opposed to MPCs), this citation cannot *necessarily and inevitably* teach administration of a population of STRO-1 expressing MPCs to induce blood vessel formation and/or repair as is required in an anticipation rejection based on inherency.

Accordingly, the Examiner's assumption that the cells disclosed in Chopp et al. *may* express STRO-1 is not a sufficient basis for an allegation of anticipation based on an inherent disclosure. Applicants respectfully direct the Examiner's attention to M.P.E.P. §2112 (referring to *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed Cir. 1993) which notes that the fact that a certain result or characteristic *may* occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. Rather, "[t]o establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is *necessarily* present in the thing described in the reference... Inherency, however, *may not be established by probabilities or possibilities*. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" (emphasis added) *See* M.P.E.P. §2112 (quoting *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted)).

Accordingly, applicants note that because Chopp et al. do not teach an enriched population of cells that express the marker STRO-1 as recited in claim 172, and claims 175-181, 183-192, and 194 dependent therefrom, the Examiner should reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §103 - Obviousness

The Examiner also alleged that claims 172, 175-181 and 183-191 are rendered obvious by the combined teachings of Chopp et al. and Jones et al., *Arthritis and Rheumatism*, 46: 3349-3360, 2002. The Examiner appears to base this rejection on the alleged disclosure in Chopp et al. of the use of MSCs to induce angiogenesis and vasculogenesis and the alleged inherent expression of STRO-1 by these cells (as discussed above) and the alleged disclosure in Jones et al., that "MSCs(MPCs)" (Examiner's phrase) express STRO-1 and other markers recited in the claims on file. Applicants further note that on page 7 of the Office Action the Examiner apparently conflates MSCs with MPCs (i.e. "neovascularization using MSCs(MPCs)").

Applicants' Response

Applicants respectfully traverse this rejection. Applicants have discussed Chopp et al. above, and maintain that Chopp et al. do not teach administration of a population of cells expressing STRO-1. Applicants further note that Chopp et al. disclose MSCs, not MPCs, and applicants have explained hereinabove that MSCs are not synonymous with MPCs (see Table 1 on page 44 of applicants' specification which shows some of the differences).

In addition, Jones et al. only characterizes expression of cell surface markers on MPCs. Jones et al. may suggest that STRO-1 has been used to detect MPCs, however Jones et al. also clearly states that this antibody is *not selective for MPCs* because the STRO-1 antigen is expressed on other cells, e.g., erythroblasts (see page 3358, left hand column). Jones et al. suggests that D7-FIB is a more suitable marker for isolating MPCs. Significantly, nowhere does Jones et al. suggest that MPCs induce neovascularization or angiogenesis.

Based on the Examiner's comments at page 9 of the Office Action, it appears that the Examiner is suggesting that it would be obvious to use STRO-1 expressing cells, e.g., as allegedly suggested by Jones et al., in the manner of using MSCs allegedly taught by Chopp et al., i.e., to induce neovascularization. However, given the teachings in the instant application that MSCs do not express detectable levels of STRO-1, as pointed out above, it appears that the Examiner is taking the position that it would be obvious to one skilled in the art to replace administering basically STRO-1 *negative* cells to induce neovascularization with administering STRO-1 *positive* cells and reasonably still expect to induce neovascularization. This is an untenable position, especially as Jones et al. do not teach any neovascularization-inducing effects of STRO-1 positive cells.

Applicants submit that it could not have been predictable at the date of the present invention based on the cited art that administration of a population of cells expressing STRO-1 would induce neovascularization. Moreover, Chopp et al., actually provides a motivation to use MSCs that may not express STRO-1 as opposed to STRO-1 expressing cells to induce neovascularization, and Jones et al. fail to provide any alternative motivation in the context of inducing neovascularization. In any event, the combination of cited references does not suggest a method of inducing formation or repair of blood vessels, wherein the method comprising the steps of culturing and/or expanding an enriched population of cells that express the marker STRO-1, and contacting said cultured and/or expanded cells to tissue in need of blood vessel formation or repair in order to generate new blood vessels or to repair existing blood vessels. Accordingly, the references cited by the Examiner fail to provide any motivation to produce the claimed invention, and fail to provide with a reasonable expectation of successfully producing the claimed invention.

Applicants also question the Examiner raising an allegation of "inherent obviousness". It is applicants' understanding that the question of inherency in a disclosure applies only to an allegation of anticipation, because obviousness cannot be predicated on what is unknown.

Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the instant rejection.